REMARKS/ARGUMENTS:

Claims 29-50, submitted hereby, are pending.

Claims 15-28 are cancelled hereby, without prejudice or disclaimer.

Present claims 29-50 contain the subject matter of cancelled claims 15-28 rewritten in order to more clearly define the instant invention. Details are provided, below, in connection with the rejection of record under 35 USC §112, second paragraph.

Claims 15-28 were rejected under 35 USC §112, second paragraph, as allegedly being indefinite. Reconsideration is requested in view of the changes to the claims effected, hereby, in conjunction with the following remarks.

Method claim 15 is amended, hereby, as present claim 29, to use the active tense in the recited method steps. As also found in claim 29, the phrase "avoiding serial tests" has been cancelled and the phrase "in a time-resolved manner" is replaced by "as a function of time." Detecting binding between the marker and phosphatidylserine in the sample "as a function of time" allows measuring the degree of apoptosis over time. For example, the degree of binding between these two substances can be detected at specific points in time, such as at 1, 2, and 5 hours after the start of the incubation step, and on one and the same sample.

The objected to phrase "characterized in that" does not appear in the present claims. It is replaced in the present claims by language more typical of United States patent practice, such as *wherein* and *comprising*.

Embodiments recited in the rejected claims after the terms *such as, especially,* and *preferably* are made the subject of separate dependent claims, i.e., present claims 31 - 34, 39 - 44, 47, and 48.

The abbreviation "PNA" used in claim 19 is replaced (in present claim 36) by "peptide nucleic acid," as disclosed in the subject application (page 9, item D). "PNA" is a well-known abbreviation (acronym) for "peptide nucleic acid" to the person of ordinary skilled in the art.

Claim 28 was rejected under 35 USC 101 as an allegedly non-statutory *use* claim. Reconsideration is requested.

None of the present claims is a *use* claim. Subject matter in claim 28 is found in present claim 50, which defines a "kit."

Claims 15-28 were rejected under 35 USC 102(b) as allegedly anticipated by journal of neuroscience methods, 86, 63-69 (1998) ("Schutte"). Reconsideration is requested.

For anticipation under § 102 to exist, each and every claim limitation, as arranged in the claim, must be found in a single prior art reference. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp.* To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis*

added). To be novelty defeating, a reference must put the public in possession of the identical invention claimed. *In re Donahue*, 226 USPQ 619 (Fed. Cir. 1985).

Claim 15 is amended, hereby, as present claim 29, to claim a "homogeneous" method, i.e., a "mix and measure" type of test. As disclosed in the subject application (page 7, 1st complete ¶):

> The cells to be examined for chemosensitivity are incubated in the presence of the substances, i.e., concurrently or with marker molecules already applied. Thus, in contrast to the heterogeneous test protocols employed to date, this is a homogeneous test of the "mix and measure" type which enables the immediate measurement of the kinetics of the apoptotic process. When annexin V is employed as the marker, it must be ensured that the calcium ion concentration remains constant and within the optimum concentration throughout the measuring time. This can be achieved, for example, by buffering the calcium ion concentration. The dependence on calcium ions can be completely circumvented by using other annexins, annexin derivatives, annexin muteins, antibodies, Fab fragments, single-chain antibodies, aptamers and/or other proteins having binding sites for phosphatidylserine as a marker instead of annexin V.

Accordingly, a cell-containing sample is incubated together with a marker and a substance, and binding of phosphatidylserine to the marker in the sample is detected as a function of time, i.e., in a time-resolved manner. Thereby, the presently claimed method enables the immediate measurement of the kinetics of the apoptotic process.

In contrast to the presently claimed "homogeneous" method, Schutte discloses a *heterogeneous* method. In accordance with the Schutte method, cells are twice washed with culture medium, in order to remove excess marker, i.e., annexin V-FITC. There is no concurrent incubation as in the presently claimed method. As taught by Schutte, apoptosis is induced by incubating cell cultures with roscovitine or okadaic acid (Schutte, page 65, §2.4). Thereafter, at several points in

time, the initial sample is split and aliquots of the cells are incubated with the annexin V-FITC marker (Schutte, page 65, §2.5; figure 3). Consequently, Schutte does not teach detection of the binding of phosphatidylserine and the marker, as a function of time, in the sample.

Accordingly, Schutte fails to describe each and every limitation as arranged in the present claims and, so, Schutte fails to anticipate the present method claims. *Jamesbury Corp., supra.*

Applicant submits that the method according to the present is beneficial compared to other described techniques, as it permits following, completely, the apoptosis process induced (in cells) by a substance, i.e., from its very early phases until secondary necrosis appears. The apoptosis-related signal, caused by the interaction between a marker and phosphatidylserine, increases over time in the initial phases apoptosis. After the onset of the secondary necrosis, the apoptosis-related signal decreases over time. Thus, only by following the induced apoptosis over its time course, as in accordance with the presently claimed invention, enables distinguishing the actual state of a particular cell population under investigation.

Other methods measure the apoptosis-related signal in a sample at a particular time after adding a substance to the sample. Accordingly, the measured signal can not be determined relative to the time course of the induced apoptosis. This inability can result in too few apoptosis-related signals, if the end-point measure is set, accidently, into the secondary necrosis phase. Prior art techniques remedy this problem by subjecting several cell samples to different incubation times or by taking aliquots from the initial sample. Such remedial procedures consume many more cell samples. In the case of clinical cell samples, a sufficient number might not be available for making

an accurate determination. This can give rise to a false diagnosis. In addition, detection of the apoptosis-related signal in several cell samples needs a calibration procedure, i.e., in order to correlate the measured signal to the number of cells included to the sample under investigation. All these time- and material-consuming procedures are unnecessary in the method presently claimed, in which a cell sample is analyzed over the complete apoptosis process in a homogeneous manner.

Request for Acknowledgment of Claims to Foreign Priority Under 35 USC 119 and Receipt of Certified Copies of Priority Documents

A claim to foreign priority under 35 USC 119 has been made (inventorship declaration, filed September 7, 2001) to each of DE19910995.9 and EP99108496.3 and certified copies of the priority documents have been received by the PTO (Notification of Acceptance, mailed September 17, 2001). In any event, the requirements of PCT Rule 17.1 having been met (Form PCT/IB304, mailed 30 August 2000, copy attached), the PTO is prohibited from requiring applicant to provide the certified copies. As set forth in PCT Rule 17.2(a) (***emphasis added***):

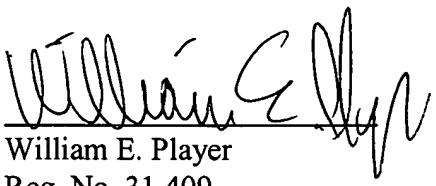
> Where the applicant has complied with Rule 17.1(a) or (b), the International Bureau shall, at the specific request of the designated Office, promptly but not prior to the international publication of the international application, furnish a copy of the priority document to that Office. *No such Office shall ask the applicant himself to furnish it with a copy.*

Accordingly, request is made that the Examiner mark the next Office Action to acknowledge each claim to foreign priority under §119 and receipt of the certified copy of each priority document.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By: 

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